Ten-Year Follow-up of Monoclonal B-cell Lymphocytosis Detected in Environmental Health Studies

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INTRODUCTION

Previous studies have reported that monoclonal expansions of B-lymphocytes can be detected in the peripheral blood of some healthy adults. The prevalence of these monoclonal expansions, recently termed monoclonal B-cell lymphocytosis (MBL), has been estimated to be as high as 5% among older adults who had a normal blood cell count. The natural history of MBL is currently unclear. Few prospective follow-up studies have investigated its propensity toward transient, stable, or progressive forms leading to B-cell chronic lymphocytic leukemia or B-cell non-Hodgkin's lymphoma.

We conducted a ten-year medical follow-up of 74 individuals with B-cell lymphocytosis, including 9 MBL cases. These individuals were identified from participants of seven environmental health studies that compared the status of the immune system among residents near hazardous waste sites with residents in comparison communities. The purpose of this follow-up study was to determine whether MBL was transient, stable, or progressive over the subsequent decade and how often B-cell lymphocytosis progressed to MBL. We also consider the potential link between MBL and residence near the hazardous waste sites.

METHODS

The base population consisted of 1,926 participants from seven cross-sectional studies conducted in the United States from 1991 to 1994. For inclusion in the base population, participants had to be at least 40 years old and have a B-lymphocyte count available from the original study. Each original study included a community near a hazardous waste site (target area) and a comparison community (comparison area). We selected 74 cases of B-cell lymphocytosis, including 9 MBL, from the base population using the selection criteria shown in Figure 1. Three individuals who had already been diagnosed with B-cell CLL or lymphoma at baseline were excluded. We obtained immunophenotypes and kappa/lambda ratios in 1997 and in 2003. We reviewed medical records and death certificates.

FINDINGS

The median age among the base population (n=1926) was 53 years, and the majority (94%) were white (Table 1). The overall prevalence of MBL was 0.57% (11/1,926), including two additional MBL cases detected during the first follow-up examination (Figure 2). Two (19%) of the 11 MBL cases developed a BLPD (case # 1026 in Figure 3 and case # 1021 in Table 2); MBL persisted without progressing to BLPD in the remaining cases followed. Compared to controls, MBL cases were older, and they were more likely to live near hazardous waste sites (age-adjusted OR=6.2; 95%CI 1.1-36.2). MBL cases had higher B-cell counts and lower T-cell counts than non-MBL cases (Table 3).

INTERPRETATION

Although only a minority of cases progressed to BLPD, these data suggest that MBL does confer an elevated risk for developing these lymphoid malignancies. It may represent a persistent and restricted innate immune response that primarily involves B-lymphocytes. Further studies are needed to distinguish stable from progressive MBL and to clarify the etiologic role of environmental exposure.

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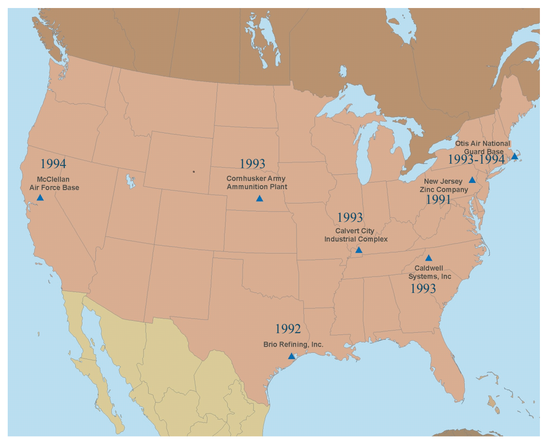

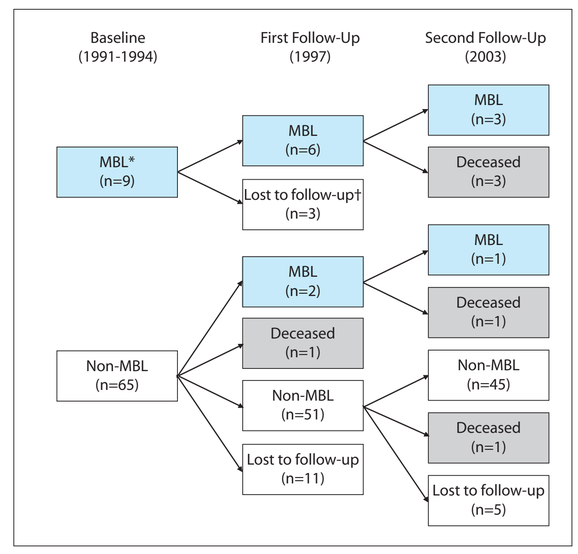

Figure 2: Medical follow-up results of the study cohort
* MBL: Monoclonal B-cell lymphocytosis as defined in Methods. † Includes participants who declined or could not be located.

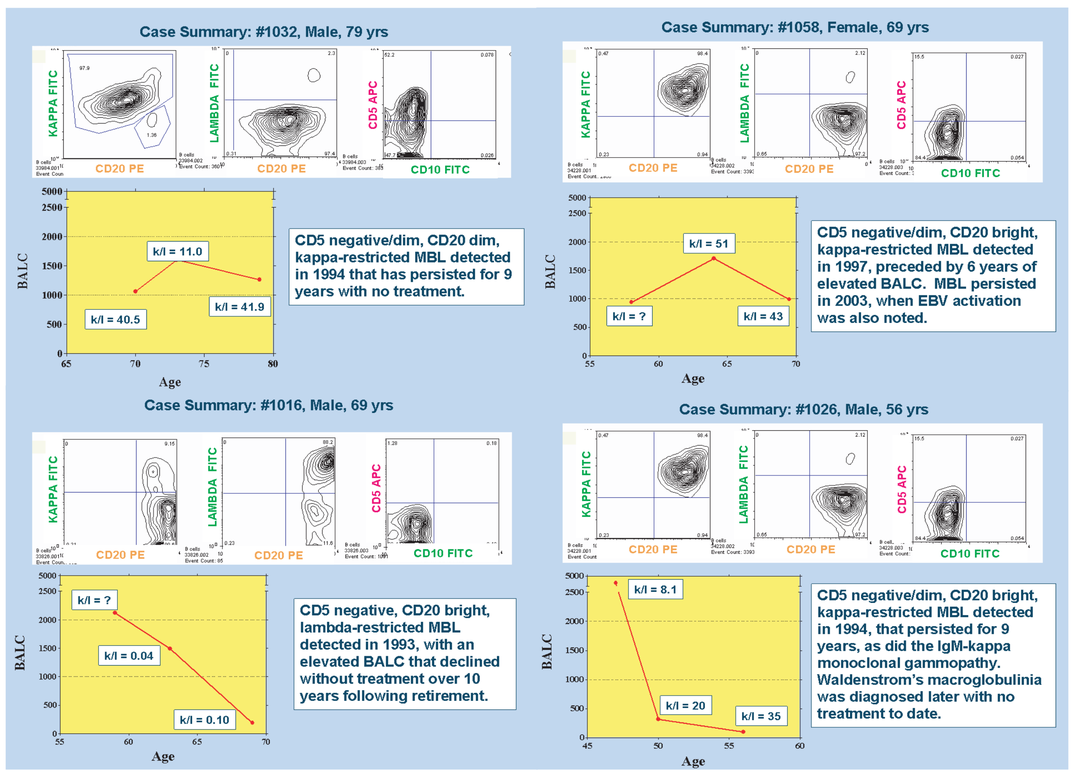

Figure 3: Clinical and laboratory characteristics of living MBL cases
k/l=kappa lambda light chain ratio. BALC=B-cell absolute count. EBV=Epstein Barr virus. The Composites of two parameter contour plots for the four MBL cases were obtained from the 2003 follow-up examination.

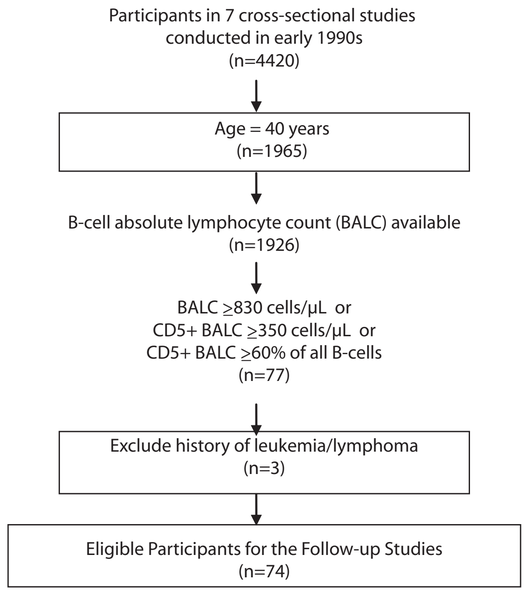

Figure 1: Selection of medical follow-up cohort

Baseline Characteristics*	Base Population* n = 1926	Eligible Participants n = 74
Age in yrs†	53 (42, 70)	52 (42, 69)
Number of Men	934 (48%)	39 (53 %)
Number of White race	1814 (94%)	68 (92 %)
Residence		
Target Area‡		
Number of participants	1124 (58%)	46 (62%)
Years of residence†	14.8 (4.0, 29.7)	15.5 (5.2, 29.8)
Comparison Area		
Number of participants	802 (42%)	28 (38%)
Years of residence†	15.1 (4.0, 31.0)	16.7 (2.0, 28.0)
White blood cell count / µL†	7400 (5400, 10 600)	9000 (6700, 12 100)
Lymphocyte count / µL†	2259 (1456, 3551)	3719 (1924, 5376)
B cell count / µL†	275 (118, 552)	887 (261, 1596)
CD5+ B cell count / µL†§	88 (30, 227)	309 (121, 735)
T cell count / µL†	1578 (944, 2566)	2124 (1193, 3309)
NK cell count / µL†‖	236 (107, 496)	293 (150, 546)

*Baseline data were obtained at the time of the original cross-sectional studies that were conducted between 1991 and1994 in the USA. The base population included the participants who were 40 years or older and had a B-lymphocyte count available at the time of the original studies. †Median (10th, 90th percentiles). ‡Target areas were near hazardous waste sites. §Based on N=771 for base population and N=41 for eligible participants. ‖Based on N=1698 for base population and N=69 for eligible participants.

Table 1: Baseline characteristics of 74 individuals eligible for medical follow-up study

Case Number	Demographic Characteristics	Case Summary
1021	Male Died in 2002 at age 78 years	CD5 bright, CD20 dim, kappa-restricted MBL detected in 1997, preceded three years by a CD5+ B-cell lymphocytosis. Severe seronegative rheumatoid arthritis was present. CLL diagnosed with a striking increase in BALC prior to death. Thrombocytopenia was noted at death, but splenomegaly and lymphadenopathy were not seen.
1022	Male Died in 2001 at age79 years	CD5 bright, CD20 dim, kappa-restricted MBL detected in 1994. Had a history of end stage, steroid dependent, COPD. Lymphadenopathy, splenomegly or lymphocytosis was never noted.
1034	MaleDied in 2002 at age 82 years	CD5 bright, CD20 dim, kappa-restricted MBL detected in 1993. Remote history of a clinical EBV infection. Atypical lymphocytes and smudge cells noted in early 2002.This patient died from a stroke.
1031	Female Died in 2002 at age 70 years	CD5 bright, CD20 bright, kappa-restricted MBL detected in 1994. This patient died from abdominal carcinomatosis.

Table 2: Case summary for deceased MBL cases

Baseline characteristics	MBL* vs. Non-MBL†: MBL n (%)	MBL* vs. Non-MBL†: Non-MBL n (%)	MBL* vs. Non-MBL†: Odds ratio§ (95% CI)	MBL* vs. Control‡: MBL n (%)	MBL* vs. Control‡: Control n (%)	MBL* vs. Control‡: Odds ratio§ (95% CI)
Age						
40-54 years	3 (27.3)	46 (73.0)	1	3 (28.3)	29 (65.9)	1
≥ 55 years	8 (72.7)	17 (27.0)	7.2 (1.7 - 30.4)	8 (72.7)	15 (34.1)	5.2 (1.2 - 22.3)
Sex						
Female	5 (45.5)	30 (47.6)	1	5 (45.5)	19 (43.2)	1
Male	6 (54.5)	33 (52.4)	1.7 (0.4 - 6.9)	6 (54.5)	25 (56.8)	0.7 (0.2 - 2.9)
Location of Residence						
Comparison area	2 (18.2)	26 (41.3)	1	2 (18.2)	22 (50.0)	1
Target area‖	9 (81.8)	37 (58.7)	2.6 (0.5 -14.0)	9 (81.8)	22 (50.0)	6.2 (1.1 - 36.2)
Absolute lymphocyte count						
< median	4 (36.4)	31 (49.2)	1	1 (9.1)	22 (50.0)	1
≥ median	7 (63.6)	32 (50.8)	1.3 (0.3 - 5.3)	10 (90.9)	22 (50.0)	9.7 (1.1 - 86.0)
Absolute B-cell count¶						
< median	2 (18.2)	31 (49.2)	1	1 (9.1)	22 (50.0)	1
≥ median	9 (81.8)	32 (50.8)	3.5 (0.7 - 18.5)	10 (90.9)	22 (50.0)	13.5 (1.5 - 125.9)
Absolute T-cell count¶						
< median	8 (72.7)	31 (49.2)	1	3 (27.3)	22 (50.0)	1
≥ median	3 (27.3)	32 (50.8)	0.2 (0.05 - 1.1)	8 (72.7)	22 (50.0)	3.8 (0.8 - 18.4)
Absolute NK-cell count¶						
< median	7 (63.6)	29 (50.0)	1	2 (18.2)	22 (50.0)	1
≥ median	4 (36.4)	29 (50.0)	0.5 (0.1 - 1.9)	9 (81.8)	22 (50.0)	3.5 (0.6 - 19.3)

*MBL: Monoclonal B-cell lymphocytosis (total n=11). †Non-MBL: Medical follow-up participants without a discernable B-cell monoclonal population (total n=63). ‡Control: A random sample drawn from the base population, excluding three cases with lymphoproliferative disease at baseline and the 74 follow-up eligible individuals, stratified by the study entry year (total n=44). §Age-adjusted for sex, location of residence, and cell counts. ‖Areas near a hazardous waste site. ¶Dichotomized cell counts, by using median values of the non-MBL group (for MBL vs. Non-MBL) and the control group (for MBL vs. Control).

Table 3: Baseline characteristics associated with the risk of MBL

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